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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,182	08/12/1999	KIM MCCLURE	PC10240A	2284

23913 7590 07/25/2003

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	21

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,182	MCCLURE ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61 and 81-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61 and 81-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Prosecution Application

The request filed on 20 May 2003 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/373,182 is acceptable and a CPA has been established. An action on the CPA follows. Claims 61 and 81-83 have now been presented for examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 61 and 81-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific compounds that are selective for TACE over MMP1, does not reasonably provide enablement for any hydroxamate compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

It is argued that the disclosure provides assays for determining the requisite selectivity of TACE over MMP1 and that the claims are limited to hydroxamate compounds. It is urged that with the teachings in the disclosure and the state of the art it would not take undue experimentation to find compounds which meet the claim limitations. Issue is taken with the previous Office actions such that "make and test" is acceptable under 112, first paragraph.

Several recent references are provided and discussed, Letavic et al. (shares instant inventorship), Levin et al. and Dunn et al., (but not made of record in a disclosure statement) which allegedly follow the teachings of the instant disclosure and find hydroxamate compounds which meet the claimed selectivity. A long list of US and foreign patents is provided allegedly supporting that inhibitors with various Q groups (like those in new claims 82-83, and recited at page 8 of the disclosure) can be produced with the subject methodology. It is not alleged that these patents demonstrate hydroxamate compounds that meet the requisite selectivity.

The issue has not been whether "make and test" is acceptable under 112, first paragraph. It has been argued only that "make and test" is not the standard. Each fact pattern must be considered with respect to the *Wands* factors determine if the scope of the claims is commensurate with the showing and reasonable guidance is provided so that undue experimentation is not required to practice the claimed invention. It is this aspect of "make and test" that is considered in determining if the legal requirements of 112, first paragraph have been met.

First, the inhibitory properties derive from the hydroxamate. This salient fact has been known for some time. What is desired is selectivity between TACE and MMP1. These two enzymes are both inhibited by hydroxamates. Hence, the hydroxamate aspect in and of itself is insufficient to establish selectivity.

Proteases cleave a polymeric structure, so typically, the active/binding sites are extended. Hence, it is well known in the art of protease enzymology, that the protease active sites not only have catalytic groups at positioned to cleave the sissile bond, but there are subsites for substrate and product recognition, especially the S1′ and P1′ subsites. It is the goal to describe and

delineate the nature of the differences in these subsites to provide the desired selectivity between different enzymes. Normally, structural information about the enzyme's subsites is needed, but it is possible to map the properties of the subsites by means of SAR studies. The classic work of Cushman and associates in mapping the angiotensin converting enzyme (ACE) site to design carboxypeptidase-like inhibitors of ACE comes to mind.

This state of the art history raises two questions. 1) Does the instant disclosure provide guidance on the structure of the subsites? 2) Are SAR studies presented that allow a person of ordinary skill in the art to map the properties of the subsites absent structural information? The answer to both of these questions is no. Clearly there is no structural information presented. There is also no consistent data presented which allows a person of ordinary skill in the art to map the subsites. What is presented is a particular scaffolding (page 7) that is modified in a nearly random manner to obtain a wide variety of modifications. As is clearly indicated in the references cited in the response, different investigators have implemented many different scaffoldings attempting, often by brute force, to find a suitable scaffolding to modify.

Duan et al., for example, present an intelligent design process where a fundamental scaffolding is modified in a systematic way with specific design objectives in mind. This is a far cry from the instant disclosure's broad and random claims of compounds with vast structural features without any clear objective. It appears from the claims that it is believed that the mere presence of the Q hydrophobic groups is sufficient structural identification to describe inhibitors with the desired selectivity. The scaffoldings used in these references are as follows: Duan et al. – γ-lactam, Levin et al. – anthranilic acid, and Letavic et al. - pipecolic acid. These scaffoldings are considerably different from each other and represent considerably different strategies. They

cannot simply be lumped together as large Q groups as apparently believed by the response. In Letivic et al., for example, the scaffolding is also modified in a non-systematic and only minimally designed fashion. The goal was to lower the overall logP and "potentially improve the physiochemical properties of the molecule". By the time of publication of Letivic et al., the structure of TACE has become available and is used therein. Hence, it cannot be said that this reference, published four years after the instantly claimed invention's date, represents state of the art at the time the invention was made.

There is no evidence in any of these references that they followed the teachings of the instant disclosure to make the "judicious choice of substituents" at the 5-position and P1′ group so as to obtain hydroxamate-based inhibitors selective for TACE over MMP1. It took years of considerable inventive contribution on the part of highly skilled artisans to obtain these hydroxamate-based inhibitors that are 110-500-fold selective for TACE over MMP1.

Applicant's arguments filed 20 May 2003 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 112, first paragraph is adhered to for the reasons of record and the additional reasons above.

New claims 82-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New claim 82 recites a long list of "substituents" exemplified by $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, etc. for which the nature and manner of the connectivity and structure of the substituents is unknown and unclear. The metes and bounds of desired structures cannot be

clearly determined. The overall structural relationship between these substituents and the hydroxamate compound of which they are a part is also unclear.

No claims are allowed.

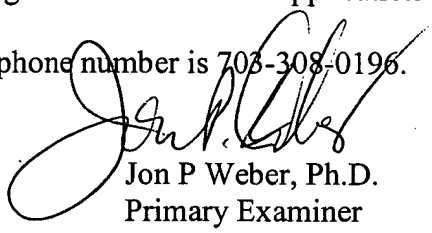
All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.53(d0. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.53(d). See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
July 24, 2003